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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,432	10/15/2001	Chen-Kun James Shen	08919-016003	3256

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EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,432	SHEN, CHEN-KUN JAMES	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response filed on 07/28/03 has been acknowledged.
Claim 51 is amended.
Claims 33-63 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121 (http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 33-36, 41-46, 51-53 and 58-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record*) in view of Miller et al (Biotechniques 7(9):980-990, 1989 *ref of record),* for the same reasons of record as set forth in the office action mailed on 04/24/03.

Zhang teaches an expression vector comprising, a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of human growth hormone (page 8502 col.1 para.4; col.2 para 2-4). The cited art teaches a HS-40 enhancer element (NF-E2/AP1-II) which comprises the nucleotide sequence of SEQ ID NO:1 (**tctgagtca**) see page 8503, fig-1B, 3'NF-E2/AP1-II. The cited art further teaches a method of expressing p-HS40 (3'NF-E2/AP1-II)-ζ597GH expression vector into isolated K562 erythroid cells. The K562 cells were transfected with expression vector and the expression of growth hormone was measured by GH assay and/or RNA primer extension assay (page 8503 fig 1 and 2). The cited art further teaches that mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer (page 8502, col.2 para.6; page 8504 fig-3).

However, Zhang does not teach a retroviral expression vector comprising a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site driving the expression of a growth hormone.

Miller teaches the making of a N2 and LNL6 based retroviral vectors comprising a promoter operably linked to a gene of interest and a polyadenylation signal, wherein the high- titre retroviral vector has been used to transduce target cells (page 984, fig-3; page 986 table-3).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to make a retroviral vector as taught by Miller, wherein the promoter and gene of interest has been replaced with a nucleic acid sequences that encodes a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone as taught by Zhang. One would have been motivated to do so because retroviral vectors has increased transfection efficiency as compared to plasmid base DNA transfection system. One would have reasonable expectation of success in doing so since making a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. In addition given the broadest reasonable interpretation to the method of expressing a transcript in a cell *(wherein the cell is an isolated cell in-vitro)* one would have reasonable expectation of success in infecting the cell in-vitro using the above described retroviral vector. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments

Applicant argues that the enhancer element (as claimed) may not function in a viral vector as suggested by McCune *(a reference cited by the applicant in support)*. Therefore Zhang and Miller would have not motivated one to make a viral vector containing an enhancer in the way suggested by the combined teaching of prior art (response page 7).

However, this is found NOT persuasive because the response element as taught by McCune is not limited to the response element as claimed i.e. SEQ ID NO:1. Furthermore, the office recognizes that obviousness can only be established by

combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Claims 37-40, 47-50, 54-57 and 60-63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (JBC 270(15):8501-8505, 1995, *ref of record*) in view of Miller et al (Biotechniques 7(9):980-990, 1989 *ref of record*) as applied to claims 33-36, 41-46, 51-53 and 58-59 above, and further in view of Jarman et al (Mol. Cell. Bio. 11(9):4679-4689, 1991; *ref of record*), for the same reasons of record as set forth in the office action mailed on 04/24/03.

Zhang and Miller are discussed in detail above. Jarman teaches a major regulatory element upstream of the human ζ-globin gene cluster, which comprises nucleotide sequences that matches 99.9% and 99.6% to the nucleotide sequences of SEQ ID NO: 2 and 3 of the instant application (page 4684, fig-5; and *the attached PTO sequence search report*). However, the nucleotide sequences as taught by Jarman do not contain point a mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca).

A retroviral vector wherein the gene of interest encodes a tissue specific ζ-globin promoter operably linked to a HS-40 enhancer and a transcriptional start site that drives the expression of a growth hormone has been found obvious to one ordinary skill in the art at the time of filing in view of Zhang and Miller as stated above. It would have been

further obvious to make a retroviral vector wherein the nucleotide sequences comprising the HS-40 enhancer region as taught by Zhang has been replaced by the nucleotide sequences as taught by Jarman. It would have been further obvious introduce a point mutation (gctgagtca to tctgagtca) in the HS-40 enhancer region (Zhang) into the nucleotide sequences as taught by Jarman. One would have been motivated to do so because changing gctgagtca to tctgagtca enhances the transcription of a gene of interest (GH) operably linked the mutated HS-40 enhancer, therefore increasing the production of GH in genetically engineered cells. One would have reasonable expectation of success in doing so, since making a point mutation and constructing a retroviral vector encoding nucleic acid sequences of interest has been considered routine in the art at the time the instant invention was made. In addition the method of expressing a transcript in an isolated cell were within the reach of one ordinary skill in the art at time of filing and one would have reasonable expectation of success in infecting the cell in-vitro using the retroviral vector as describe above. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments

Applicant argues that Zhang and Miller do not suggest a viral vector containing an enhancer. Jarman teaches a regulatory element of the human a globin gene. This element contains nucleotide sequences that are 99.9% and 99.6% identical to SEQ ID N0: 2 or 3. Jarman does not suggest making a viral vector containing the regulatory elements as claimed.

However, this is found NOT persuasive because Zhang clearly teaches that a mutant HS-40 enhancer with 1-bp mutation in the 3'NF-E2/AP1 motif (gctgagtca to tctgagtca) exhibited a 2-3 fold higher level of enhancer activity than the wild type HS-40 enhancer. Therefore, it would have been obvious introduce a point mutation (gctgagtca to tctgagtca) in the HS-40 enhancer region (Zhang) into the nucleotide sequences as taught by Jarman. Zhang clearly provide the motivation to make a single nucelitide change in order to enhance gene expression. Furthermore one would have a reasonable expectation of success, since making a point mutation and constructing a retroviral vector encoding the mutated nucleic acid sequences of interest has been

considered routine in the art. Therefore considering the combined teaching of cited prior art the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838 (**571-272-0769**). The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel Ph.D. can be reached on 703-305-1998 (**571-272-0781**). The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
Patent examiner

JEFFREY FREDMAN
PRIMARY EXAMINER